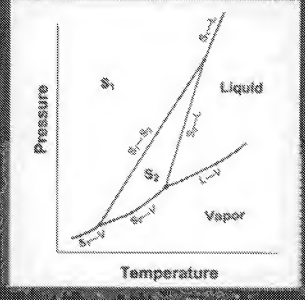
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 95

# Polymorphism in Pharmaceutical Solids

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drate. Both urapidil [58] and dehydroepiandrosterone [59] were found to exhibit complex polymorphic/solvate systems, but the relative enthalpy of these could be deduced through the use of solution calorimetry. As an example, the data reported for urapidil [58], which have been collected into Table 4, show that the form with the lowest heat of solution consequently has the highest enthalpy. In this particular case, the rank order of enthalpy changes corresponds to that of the free energy changes.

It is invariably found that the amorphous form of a compound is less stable than its crystalline modification, in the sense that the amorphous form tends to crystallize spontaneously, indicating that the amorphous form has the greater Gibbs free energy. As discussed in Chapter 1, the amorphous form is more disordered and must therefore have a greater entropy than does the crystalline form. Hence the enthalpy of the amorphous form is also greater. The heat of solution of amorphous piretanide in water was found to be 12.7 kJ/mol, while the heat of solution associated with Form C was determined to be 32.8 kJ/mol [60]. The authors calculated the heat of transformation associated with the amorphous-to-crystalline transition to be −20.1 kJ/mol. Any facile transformation of the two phases was obstructed by the significant activation energy (145.5 kJ/mol).

As emphasized above, a basic thermodynamic understanding of

**Table 4** Heats of Solution in Water for the Various Polymorphs and Solvates of Urapidil

| Crystalline form | Heat of solution (kJ/mol) |
|---|---|
| Form I | 21.96 |
| Form II | 24.26 |
| Form III | 22.98 (estimated) |
| Monohydrate | 44.28 |
| Trihydrate | 53.50 |
| Pentahydrate | 69.16 |
| Methanol solvate | 48.39 |

*Source*: Ref. 58.